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Correlation of Tinnitus Severity Index and Tinnitus Handicap Inventory with Hematological Parameters in Patients with Subjective Tinnitus

Demet Yazici[1] Mehmet Celalettin Cihan[2]

[1] Department of Otorhinolaryngology, Adana City Training and Research Hospital, Adana, Turkey.
[2] Department of Audiology, Cappadocia University, Nevşehir, Turkey.

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Address for correspondence Demet Yazici, MD, Adana Şehir Egitim ve Arastirma Hastanesi, Kulak Burun Boğaz Kliniği, Serinevler Mah, Ege Bağatur Bulvarı Üzeri Yüreğir, Adana, Turkey (e-mail: demetyazici@yahoo.com).

Abstract

Introduction Tinnitus etiopathogenesis is still unclear and treatment options are controversial despite current advances in medicine.

Objectives To analyze the correlation between patients' symptom scores, systemic inflammation, and trombosis biomarkers.

Methods In this prospective study, we evaluated the degree of complaints of subjective tinnitus patients with the tinnitus severity index (TSI) and tinnitus handicap inventory (THI), and correlated these symptom scores with hematological parameters such as the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), mean thrombocyte volume (MPV), and platelet distribution width (PDW).

Results A total of 44 patients with subjective tinnitus, 25 (56.8%) men and 19 (43.2%) women, were included in this study. The mean age of the patients was 42.3 ± 14.8 years. When the correlation between TSI and NLR, PLR, PDW, and MPV values of the patients were analyzed, no statistically significant correlation was found between TSI, NLR, and PLR ($p > 0.05$). However, there was a statistically weak positive correlation between TSI, MPV, and PDW.($p < 0.05$). When the correlation between THI and NLR, PLR, PDW, and MPV values of the patients were analyzed, no statistically significant correlation was found between THI, NLR, and PLR ($p > 0.05$). There was a statistically weak positive correlation between THI, MPV, and PDW ($p < 0.05$).

Conclusion We were unable to detect any relationship between systemic inflammation markers (NLR and PLR) and symptom scores, but a weakly positive correlation was observed between thrombosis markers (MPV and PDW) and symptom scores, and as the subclinical thrombosis markers elevated, so did the symptom scores.

Keywords
- tinnitus
- subjective tinnitus
- correlation
- inflammation
- thrombosis

Introduction

Tinnitus is derived from the Latin verb "tinnio" meaning "ringing in ears". It is defined as a sound heard by the patient without any external stimulus. Tinnitus may be heard in the right, left, or both ears; it may cause insomnia, be associated with various psychiatric diseases, and be accompanied by hearing loss. The sounds can be in the form of humming,

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buzzing, singing, and playing music. In this condition, there is no meaning in sounds patients hear, which is how it is distinguished from auditory hallucinations that accompany psychiatric diseases. Tinnitus is divided into subjective and objective types. In subjective tinnitus, which is more common, only the patient hears sound, while in the objective type, the sound heard by the patient can also be heard by others.[1]

The incidence of tinnitus in the population increases with age, and it is one of the main reasons for visits to ear, nose, and throat (ENT) clinics. The etiopathogenesis of tinnitus has not yet been fully revealed, and many studies are still being conducted on it. Patient satisfaction with treatment is generally low, with limited options, and studies on this theme are still developing.[1,2]

The neutrophil/lymphocyte ratio (NLR) is obtained by dividing the number of neutrophils in peripheral blood by the number of lymphocytes and the platelet/lymphocyte ratio (PLR) is a ratio obtained by dividing the platelet count by the lymphocyte count, and they both indicate inflammation.[3,4] The mean platelet volume (MPV) gives information about the platelet size in the systemic circulation and is used to evaluate platelet disorders; the platelet distribution width (PDW) indicates the heterogeneity of platelets in the systemic circulation. MPV and PDW correlate with each other and are associated with thromboembolic events.[5]

As animal blood values differ greatly, neutrophil-lymphocyte ratio (NLR) is a ratio that has been used in the veterinary field for many years.[4] Zahorec et al. observed that in critically ill patients, neutrophils increased and lymphocytes decreased depending on the amount of stress and immunological endurance, and suggested NLR as a simple and rapid test that could detect systemic inflammation.[3] Additionally, they purposed that the increase in neutrophils depended on the increase in neutrophil demargination from the endothelium, the decrease in neutrophil apoptosis and the effect of growth factors on stem cells, also pointing out the cause of lymphopenia as suppression of cellular immunity.[3,6,7] Walsh et al. stated that NLR could be used as a prognostic factor that indicates systemic inflammation in colorectal cancer patients, thus paving the way for the use of NLR in many cancer types.[8] Gibson et al. showed that NLR can be used to detect low-grade inflammation that triggers atherosclerosis, and that high values of it are associated with lower survival after coronary artery bypass surgery, which showed that this parameter can be associated with cardiac diseases.[9] After 2010, studies on NLR have increased, especially on various types of cancer and heart diseases, as well as studies related to immunological, neurological, and allergic diseases have been added to the literature.

Activated platelets play an important role in both chronic inflammation and thrombosis. In the last 10 years, there have been many publications studying the role of platelets as a biomarker in cardiovascular diseases, tumoral and immunological diseases. The MPV, as the name suggests, is a simple and inexpensive laboratory measurement of platelet volume. Various publications in the literature shows that increased or decreased MPV is associated with various thrombotic and inflammatory events.[10–12] The PDW is a routine laboratory measurement that measures the heterogeneity of platelets in peripheral blood. Increased PDW values indicate increased platelet heterogeneity and are used as a biomarker of various inflammatory and thrombotic events. Simultaneously, increased PDW and MPV indicate increased platelet activity.[5] Increased PDW and MPV is associated with an increased risk of inflammation, thrombosis, stroke and mortality.[13–15]

In this study, the severity of subjective tinnitus was evaluated using psychosomatic tests, the tinnitus severity index (TSI) and tinnitus handicap inventory (THI), and correlation between them and the NLR, PLR, MPV, and PDW were analyzed.

Material and Method

Patients who were referred to our ENT clinic with complaints of tinnitus between July 2020 and May 2021 were included in this study. The inclusion criteria consisted of patients over 18 years of age, having bilateral or unilateral subjective tinnitus for at least 3 months without pathological findings in ENT examination. Patients with a history of sudden hearing loss, acoustic trauma, otologic surgery, systemic disease, or asymmetric hearing loss on the audiogram were excluded from the study. The power of this study was calculated at 94%, using the G*Power (Heinrich Heine University, Düsseldorf, NRW, Germany) software with $\alpha = 0.05$ type I error, $\beta = 0.10$ type II error and effect size 0.5.

The ethical approval of this study was obtained from the Medical Research Ethics Committee of our university (2020/14). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on the Helsinki Declaration of 1975, as revised in 2008.

Data were analyzed with the Statistical Package Social Sciences (SPSS, IBM Corp. Armonk, NY, USA), version 23.0. Compliance with homogeneous distribution was examined using Shapiro-Wilk and Kolmogorov-Smirnov tests. The Spearman ρ correlation coefficient, Pearson correlation coefficient, independent two-sample t-test, and Mann-Whitney U test were used for statistical analysis. Analysis results were presented as mean ± standard deviation and median (min–max) for quantitative data. The significance level was taken as $p < 0.05$.

After obtaining the informed consent form all participants, the tinnitus severity index (TSI) and tinnitus handicap inventory (THI) questionnaire were applied to the patients.

1. Tinnitus Severity Index (TSI):

The tinnitus severity index measures the negative effects of tinnitus on patients' life, its lowest score is 12 and the highest is 60. Patients are classified according to their total scores, with values from 1 to 12 points being very mild, 13 to 24 points as mild, 25 to 36 points as moderate, 37 to 48 points as severe, and 49 to 60 points as catastrophic (extreme) degree.

2. Tinnitus Handicap Inventory (THI)

The tinnitus handicap inventory (THI) is a 25-item questionnaire that is widely used to measure symptom severity and

determine the degree of disability. The lowest score is 0 and the highest is 100. Patients are classified according to their total scores, with values from 1 to 16 points as grade 1–slight, 18 to 36 as grade 2–mild, 38 to 56 as grade 3–moderate, 58 to 76 as grade 4–severe, and 78 to 100 points as grade 5–catastrophic degree.

Results

A total of 44 patients met the study criteria and were included. There were 25 (56.8%) male and 19 (43.2%) female participants, with ages ranging from 18 to 66 years, with a mean of 42.3 ± 14.8 years. The male patients' age ranged from 19 to 65 years (43.2 ± 14.8 years), and for female patients it ranged from 18 to 66 years (41 ± 15.1 years). When male patients and female patients were compared in terms of age, no statistically significant difference was found ($p = 0.32$).

The mean TSI score of the patients was 41.9 ± 10.2, and the mean THI score was 59.6 ± 22.8. When patients were evaluated according to their TSI scores, 1 (2.3%) was in the category of mild, 13 (29.5%) were moderate, 17 (38.6%) were severe, and 13 (29.5%) were extreme grade. According to THI scores, 9 (20.5%) of the patients were mild, 11 (25%) were moderate, 9 (20.5%) were severe, and 15 (34.1%) were catastrophic.

When male and female patients were compared in terms of TSI scores, THI scores, neutrophil, lymphocyte, and platelet counts, as well as NLR, PLR, PDW and MPV, no significant difference was found between them. (►**Table 1**)

Considering the correlation between the ages of the patients and TSI ($p = 0.716$) and THI ($p = 0.875$), no significant relationship was found between them.

The correlation between patients' TSI and THI scores and NLR, PLR, PDW, and MPV values was evaluated. There was a statistically weak positive correlation between TSI score and PDW ($r = 0.386$; $p = 0.01$), and MPV ($r = 0.389$; $p = 0.009$). Additionally, a statistically weak positive correlation was observed between THI scores and PDW ($r = 0.366$; $p = 0.015$), and MPV ($r = 0.362$; $p = 0.016$). No statistically significant correlation was found between TSI and THI scores and the other variables ($p > 0.05$). (►**Table 2**)

Discussion

When we analyzed patients in terms of gender and age, we observed tinnitus was most common in male patients of the 6th decade. Bhatt et al., in their study, ascertained that subjective tinnitus was more frequent in men over 60-years-old, and male patients asking for physician consultations on this disease were more common , as tinnitus had a more serious impact on quality of life with increasing age.[16] In a study by Dawes et al., this disease was again detected most frequently in men over 60-years-old, but tinnitus disturbance was more prevalent in female patients.[17] An epidemiological study by Lee et al. demonstrated tinnitus gradually increased with age and was most common in women over 80-years-old.[11] A prevalence study by

Table 1 Comparison of variables by gender

	Male		Female		Total		Statistical tests	*p*-value
	$\bar{x} \pm \sigma$	Median (min–max)	$\bar{x} \pm \sigma$	Median (min–max)	$\bar{x} \pm \sigma$	Median (min–max)		
TSI	41.8 ± 10.2	43 (26–56)	42.1 ± 10.5	42 (20–59)	41.9 ± 10.2	42.5 (20–59)	U = 239.0	0.972
THI	59.7 ± 22.4	60 (22–90)	59.5 ± 24	60 (20–96)	59.6 ± 22.8	60 (20–96)	U = 243.0	0.896
Neutrophil	4.2 ± 0.9	4.2 (2.8–5.6)	4.4 ± 1.6	4.3 (1.8–8.3)	4.3 ± 1.3	4.3 (1,8–8.3)	t = −0.402	0.69
Lymphocyte	2.1 ± 0.6	2.1 (1.1–3.4)	2.3 ± 0.9	2.3 (0.9–4.4)	2.2 ± 0.8	2.1 (0.9–4.4)	t = −0.991	0.327
Platelet	231.6 ± 48.3	221 (176–347)	242.7 ± 77.9	223 (123–410)	236.4 ± 62.2	221.5 (123–410)	U = 257.5	0.636
PDW	17 ± 0.4	17 (16.3–17.7)	17.1 ± 0.6	17 (15.8–18)	17.1 ± 0.5	17 (15.8–18)	t = −0.652	0.518
MPV	8.9 ± 0.6	8.8 (7.5–10.4)	9.5 ± 1.1	9.3 (7.2–11.3)	9.1 ± 0.9	9 (7.2–11.3)	t = −2.003	0.055
NLR	2.2 ± 0.7	2.2 (1.1–3.7)	2.2 ± 1.1	1.6 (0.8–4)	2.2 ± 0.9	2 (0.8–4)	U = 210.5	0.522
PLR	118.8 ± 32.9	112.9 (58.7–178.2)	116.9 ± 47.2	98.2 (61.4–232.2)	118 ± 39.2	107 (58.7–232.2)	U = 204.0	0.427

Abbreviations: MPV, mean thrombocyte volume; NLR, neutrophil/lymphocyte ratio; PDW, platelet distribution width; PLR, platelet/lymphocyte ratio; THI, tinnitus handicap inventory; TSI, tinnitus severity index.
Notes: $\bar{x}$, mean; σ, standard deviation; t, independent samples t-test; U: Mann-Whitney U test.

Table 2 Correlation between TSI and THI scores and quantitative data

	TSI		THI	
	r	*p*-value	R	*p*-value
Neutrophil[a]	−0.036	0.816	−0.098	0.526
Lymphocyte[a]	−0.264	0.084	−0.265	0.082
Platelet[b]	−0.067	0.665	−0.026	0.868
PDW[a]	0.386	**0.010**	0.366	**0.015**
MPV[b]	0.389	**0.009**	0.362	**0.016**
NLR[a]	0.242	0.113	0.185	0.229
PLR[b]	0.111	0.474	0.197	0.199

Abbreviations: MPV, mean thrombocyte volume; NLR, neutrophil/lymphocyte ratio; PDW, platelet distribution width; PLR, platelet/lymphocyte ratio; THI, tinnitus handicap inventory; TSI, tinnitus severity index.
Notes:[a] Pearson correlation coefficient.[b] Spearman correlation coefficient.

Wu et. al. observed that tinnitus is more intense in men of European origin, and complaints over the age of 65 increased by 3 times compared to other age groups.[18] In the study by Günay et al., tinnitus was more frequent in men than in women (37.5% and 27.4%), but they did not detect an effect of age on disease frequency.[19] As seen, many studies have been conducted on the prevalence of tinnitus and have found that it is more prevalent in older men. Various studies linked this result to the noise exposure that men experience in the workplace environment and accompanying diseases.

In the literature, it has been suggested that some metabolic and endocrine diseases cause inflammation and thrombosis, affecting the cochlear microcirculation and creating microinfarctions, damaging hair cells and increasing spontaneous activity, developing abnormal synapses in neuronal cells and misinformation in the auditory cortex, and causing tinnitus.[20,21] Smoking causes oxidative damage in the inner ear; and hypertension, diabetes mellitus, and various cardiovascular diseases increase thrombosis, thus affecting cochlear microcirculation. Anemia leads to hemodynamic changes, therefore increasing heart rate and causing cellular destruction in the inner ear, by decreasing oxygen transport. Hyperlipidemia impairs the movement of outer hair cells. It has been suggested that various autoimmune diseases may cause tinnitus by affecting the cochlear flow with inflammatory mediators.[20–23]

Various studies have shown that simultaneous increases in MPV and PDW are associated with increased platelet activity and aggregation.[5,24–26] It is emphasized that increased MPV and PDW values may cause tinnitus by disrupting cochlear microcirculation, but further studies on pathogenesis are required.[27]

In this study, the mean TSI score of the patients was 41.9 ± 10.2, and the mean THI score was 59.6 ± 22.8. Both the mean of TSI and THI scores were in the severe category. No statistical difference was found between male and female patients considering TSI and THI scores, in terms of degree of complaint. Furthermore, the relationship between age and increased symptom scores, as seen in other studies, was not found in this study.[11,17]

The correlation between patients' TSI and THI scores and NLR, PLR, PDW, and MPV values was evaluated. There was no statistically significant correlation between TSI and THI scores and NLR and PLR, but a weak positive correlation was found between both tests and PDW and MPV.

There are various articles in the literature that evaluate the relationship between tinnitus and hematological parameters from different perspectives. They are generally case-control studies, and few evaluate symptom scores.[28–32] In the case-control study conducted by Ozbay et al., severe tinnitus patients, with at least 2 weeks of symptoms, and THI scores of 3 to 5 were included. Patients with stage 1 and 2 were not included due to their low-grade complaints of tinnitus. Compared to healthy patients, they found that NLR was higher in those with severe tinnitus.[33] In the case-control study of Ulusoy et al., a statistically significant difference was found between the patient and control groups in terms of MPV and PDW values, regardless of tinnitus severity.[31] In the study by Bilal et al., no significant difference in NLR, PLR, and MPV/lymphocyte ratios were detected between the patient and control groups, and when patients were divided into 5 stages according to THI scores.[30] Yildiz et al. found that MPV and NLR values were higher in the patient group, and NLR values above 2.17 increased the risk of tinnitus 1.991 times.[34]

There are many conflicting case-control studies examining the relationship between tinnitus and hematological parameters. The degree of tinnitus was evaluated in very few of them, and many studies were conducted on the presence and absence of tinnitus. Yuksel et al. classified patients into 5 groups according to THI scores, but there were no stage 5 catastrophic patients, unlike in our study. Furthermore, when they analyzed the difference between PDW, MPV, and platelet counts of the 4 groups of patients, no statistically significant difference was observed.[35] In the study of Sarikaya et al., MPV was significantly higher in the patient group; however, when the patients were classified by tinnitus characteristics (frequency, definition, duration), no difference was found in terms of MPV values. They also stated that MPV values should be evaluated according to the severity of the disease, and that was considered as the limitation of the study.[36] In our study, when the correlation between TSI and THI scores, the severity of the disease, and PDW and MPV was investigated, a statistically significant weak positive correlation was found as a result.

Conclusion

In this study, the correlation between patients' complaint levels, systemic inflammation biomarkers, and systemic coagulation biomarkers was examined, and the effects of inflammation and thrombosis on tinnitus symptom scores were discussed. In conclusion, there was no statistical relationship between systemic inflammation markers, NLR, and PLR and symptom scores. A statistically significant, weak, positive correlation was observed between MPV and PDW and symptom scores.

Furthermore, as symptom scores increased so did the thrombosis markers. This study supports the theory that thrombosis may cause tinnitus by affecting the cochlear microcirculation. As our patient group is limited, conducting future studies with an increased sample will also increase the study's validity.

Financial Disclosure
None.

Conflict of Interests
The authors have no conflict of interests to declare.

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